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CONTROLLED RELEASE OF MACROMOLECULES FROM POLYMERS

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INTRODUCTION

Pharmaceutical, biological, and agricultural applications of sustained-release polymers continue to increase in scope and importance. The ability to release molecules in a continuous and controlled manner, however, is often limited by the vehicles used and the methods of drug incorporation. Until 1974, all slow-release systems were limited by the inability to continuously deliver macromolecules (M.W. >1000) from polymers. Since then, we have overcome this limitation and developed new methods for the sustained release of macromolecules. In this report, we present a brief history of sustained-release polymers and discuss the development, application, and control parameters of macromolecular delivery systems.

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EARLY HISTORY OF SUSTAINED-RELEASE POLYMERS

Although the principle of slow release has been utilized since 1950 in both the pharmaceutical and agricultural industries, it was not until the mid-1960's that polymers were used for the slow release of molecules. Folkman and Long (1) first reported sustained drug release from polymers in 1964. The idea came from two separate experiments. Folkman was using thyroid hormone to treat experimental heart block in animals and sought a means of continuously releasing this drug. Long was studying the turbulence induced in water flowing around silicone rubber heart valves. For photographic purposes, he stained the heart valves and found that certain dyes, such as rhodamine and Sudan III (i.e. oil-soluble dyes), would diffuse into silicone rubber, whereas water-soluble dyes, such as methylene blue, would not.

It was then found that rhodamine or Sudan powders placed inside the lumen of a silicone rubber tube would diffuse through the tube's wall for months. A variecy of drugs were then tested using this silicone rubber system. In general, low molecular weight (<1000) and non-polar substances diffused through silicone, whereas polar and high molecular weight substances did not (1).

After this discovery, other investigators reported that silicone rubber and other polymers could continuously deliver a variety of drugs (2-4). By 1970, there were nearly two dozen studies of polymer-drug sustained-release systems. However, all of these were limited to low molecular weight drugs and most required that the drug be lipid-soluble.

The first report of sustained release of macromolecules was from Davis in 1972 (5,6). In his studies, polyacrylamide and polyvinylpyrrolidone were used as vehicles. However, these polymers were inflammatory and permitted only brief periods of sustained release (7). In our laboratory, Gimbrone and co-workers also reported the use of polyacrylamide as a vehicle for sustained release of macromolecular tumor proteins (8). Nevertheless, despite attempts to eliminate inflammation by exhaustive washing and other means, polyacrylamide still caused tissue damage (8).

In 1974, we focused our attention on several new polymers: poly-2-hydroxyethylmethacrylate (polyHEMA or Hydron), polyvinylalcohol, and ethylene-vinylacetate copolymer; and on new methods of drug incorporation to achieve sustained macromolecular release. In our original work (7), we found that if the above polymers were dissolved in appropriate solvents, mixed with powdered or dissolved macromolecules, and then dried, the resulting pellets were capable of continuous release. With ethylene-vinylacetate copolymer, proteins were

released in biochemically active form for over 100 days. However, although sustained release had been established, two important considerations remained. First, the ability of these polymeric systems to operate effectively *in vivo* had to be demonstrated. Second, it was essential to develop reproducible methods for fabricating these delivery systems and to elucidate the factors controlling release kinetics. In the following sections, we review our initial developmental work on macromolecular polymeric delivery systems and discuss our studies in both of these areas.

INITIAL STUDIES ON MACROMOLECULAR DELIVERY SYSTEM POLYMERS

In our early studies, we examined a variety of polymers for both biocompatibility and sustained release. Polyacrylamide and polyvinylpyrrolidone (20%, w/v) were prepared in sterile glass petri dishes as described by Davis (6). PolyHEMA, polyvinylalcohol, and ethylene-vinylacetate copolymer (40% by weight vinylacetate; Elvax 40) in powder or pellet form were gifts from the ALZA Corporation. Polyvinylalcohol and ethylene-vinylacetate copolymer were washed in 2.5% (w/v) reagent-quality, absolute, pure, ethyl alcohol (USP) at 37°C in sterile roller bottles. One hundred changes of alcohol were made, with a minimum of 3 hrs. per wash. After the final wash, the alcohol was decanted and the wet polymer was poured into a sterile glass petri dish; the remaining alcohol was removed by vacuum drying. The alcohol wash removed various impurities that are inflammatory in normal tissues (e.g. antioxidants). This process also sterilized the polymers (9).

Biocompatibility

The cornea was used to study the host response to the polymers; it is the most sensitive of all indicators of inflammation. The cornea's clarity and avascularity permit stereomicroscopic observation of inflammatory characteristics: edema, white cell infiltration, and neovascularization (7,10).

Sterile polymer pellets (1.5 x 1.5 x 0.5 mm) were implanted within the corneal lamellae of 2 to 3-month old New Zealand white male rabbits by aseptically creating intracorneal pouches (8). Using a Wheeler cyclodialysis spatula and fine forceps, the pellets were placed at the lower edge of the pouch within 1 to 2 mm of the vessels of the corneal-scleral

junction. Corneal implants were examined four times weekly over 2-month periods with a slit-lamp stereomicroscope at 6 to 40x magnification. The corneas were fixed in 10% buffered formalin and stained with hematoxylin and eosin for histological examination.

Only corneas containing polyHEMA or alcohol-washed ethylene-vinylacetate copolymer were completely free of inflammation. In 35 experiments, no inflammatory characteristics were detected stereomicroscopically (7). Histologic sections taken 3 to 4 weeks after implantation showed no foreign cells in the region surrounding the polymer or other areas of the cornea (Figure 1a).

FIGURE 1. (a) Histologic section of rabbit cornea containing washed ethylene-vinylacetate copolymer. Section is stained with hematoxylin and eosin. The polymer dissolved in the fixative, but a hole remains where the polymer was. Note the lack of distortion of normal corneal structure and the lack of a host response to the implant.

In contrast, polyacrylamide and polyvinylpyrrolidone, particularly the latter, caused significant inflammation (Figure 1b). Repeated stereomicroscopic and histologic examinations consistently showed that both polymers caused substantial tissue damage (9).

FIGURE 1. (b) Histologic section of rabbit cornea containing polyacrylamide gel at the same magnification as in (a). The black dots represent inflammatory cells. The increased width of the cornea is representative of edema.

Demonstration of Long-term Release

In our original studies, slow-release pellets were made by first dissolving polymers in appropriate solvents: polyHEMA in absolute alcohol at 37°C; ethylene-vinylacetate copolymer in methylene chloride at 37°C; and polyvinylalcohol by autoclaving in distilled deionized water. With ethylene-vinylacetate copolymer, macromolecules were in powdered form; for the other polymer systems, macromolecules were either

powdered or in aqueous solution. One hundred to 500 µl of polymer solution was mixed with the macromolecules to be released, and a small amount of the resultant mixture was placed in conical molds 2 mm in diameter and 1.5 mm deep. The molds were then dried under vacuum overnight, which caused the solvent to evaporate with the macromolecules trapped within the polymer matrix. The dried polymer was hydrated by adding a drop of lactated Ringer's solution, and gently removed from the mold. The entire procedure was simple, rapid, sterile, and performed at room temperature (7).

To examine kinetics, we incorporated different proteins into polymers and measured the rate of protein release using the Lowry protein assay (7). We found that the rate of protein release depended on the polymer concentration in solution during casting and on the type of polymer used (7). In initial trials with soybean trypsin inhibitor (M.W. 21,000), protein was released rapidly from polyHEMA, somewhat more slowly from polyvinylalcohol, and least rapidly from ethylene-vinylacetate copolymer (Figure 2). In a subsequent test, four different proteins, ranging in molecular weight from 14,000 to 250,000, were continuously released from ethylene-vinylacetate copolymer for over 100 days (Figure 3).

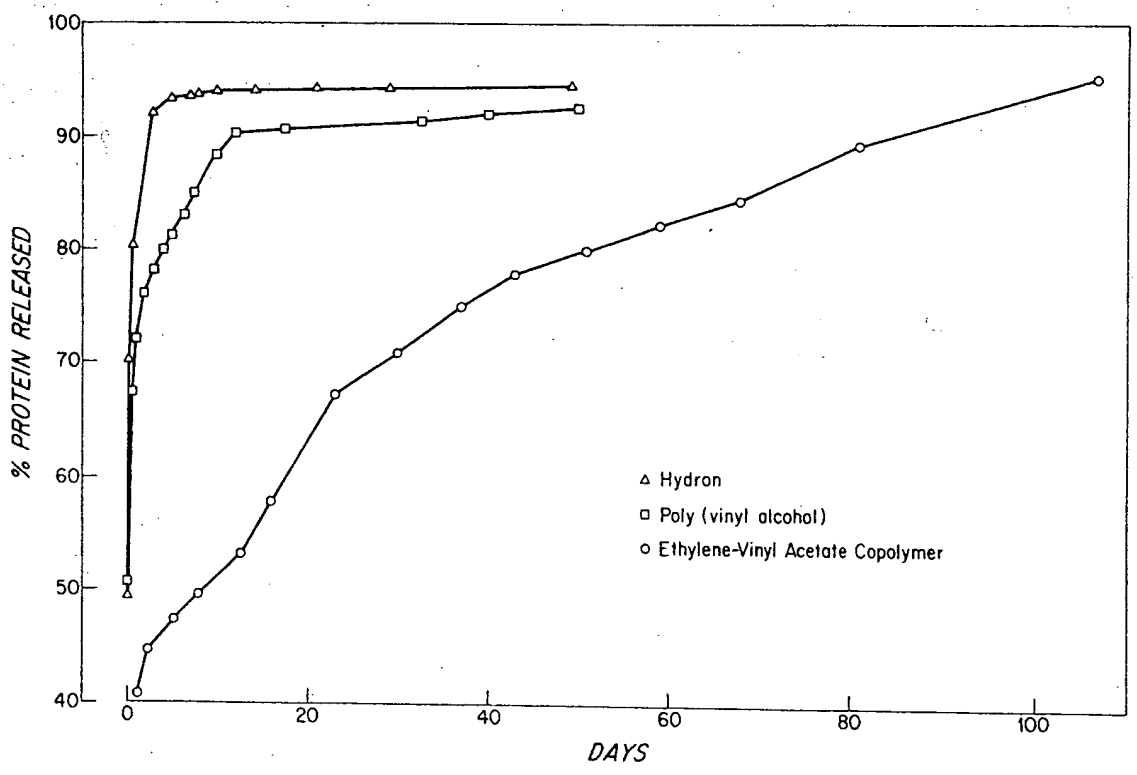

FIGURE 2. Release of soybean trypsin inhibitor from coated polymer pellets. Protein concentrations in polymer solutions were all 50 mg/ml when cast.

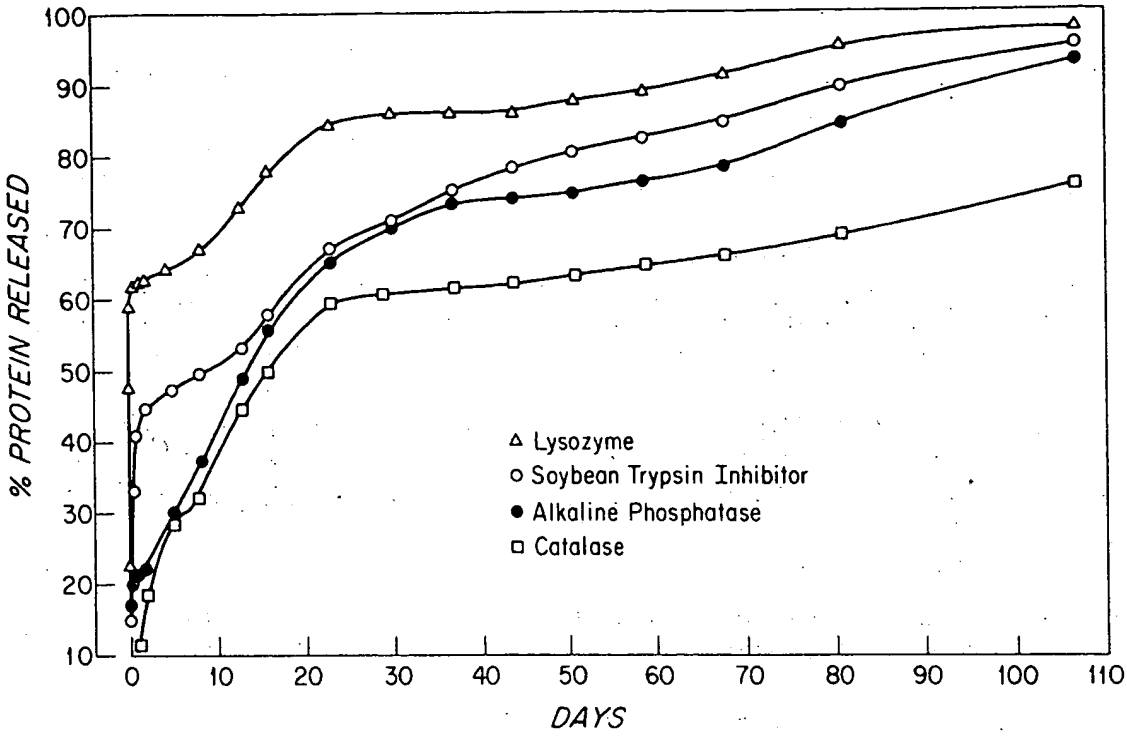

FIGURE 3. Protein release from coated ethylene-vinylacetate copolymer pellets. Protein concentrations in polymer solutions were all 50 mg/ml when cast.

Demonstration of Release of Biochemically Active Material

Polymers containing 300 µg of soybean trypsin inhibitor, lysozyme, or alkaline phosphatase were tested for release of biochemically active protein. Polymers were incubated in 20 ml volumes of lactated Ringer's solution at 37°C. The solution was changed five times during the first day of incubation, daily each of the next nine days, and every two days during subsequent incubation (10). Before each change, the polymer was blotted dry on an absorbent tissue to remove adherent solution, and then washed with additional Ringer's solution. Polymers were removed periodically from incubation, washed with Ringer's solution, and placed in wells on specialized agar slides, an example of which is shown in Figure 4 (for lysozyme). When tested in this fashion, ethylene-vinylacetate copolymer pellets continued to produce zones on these slides for over 100 days, indicating that the pellets were releasing nearly 1 µg/day of biochemically active protein (9). Furthermore, when the specific activity of alkaline phosphatase was tested before and after incorporation

into each of the three polymers, more than 80% of the enzyme escaping was active. We also have conducted studies with other macromolecules (non-proteins), such as heparin and DNA, and found that they are continuously released from ethylene-vinylacetate copolymer *in vitro* for periods of months (7).

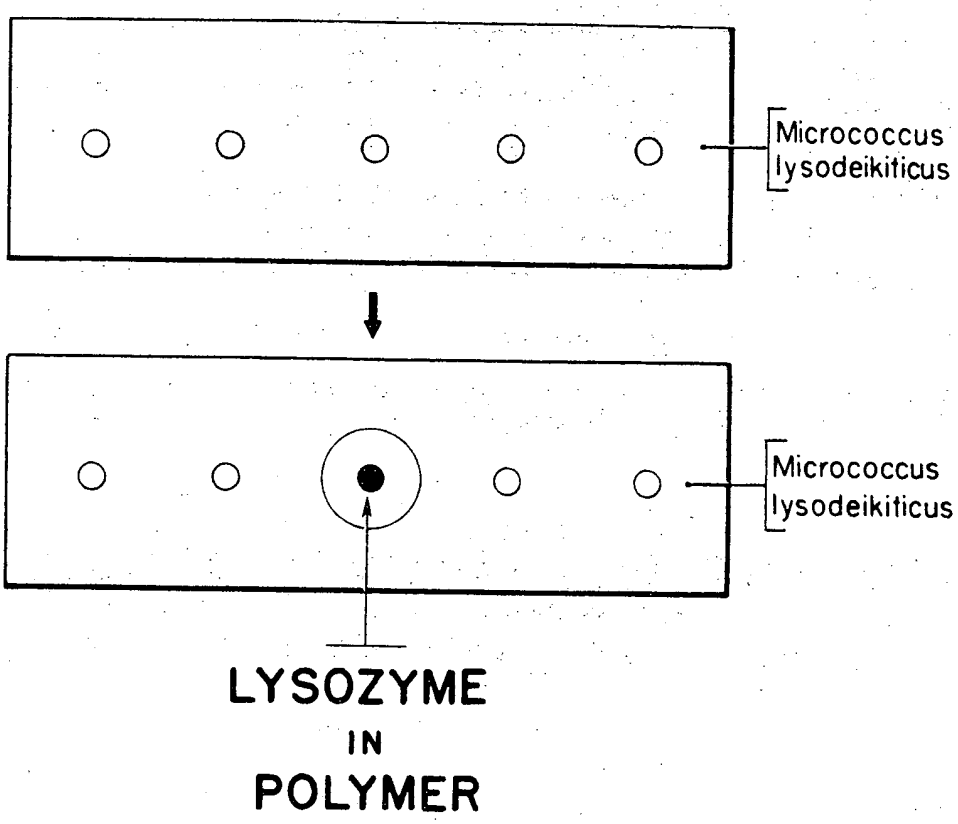

FIGURE 4. Agar slide used to assay lysozyme. The slide contains 1% agar and 0.03% Micrococcus lysodeikiticus in 0.05 M phosphate buffer, pH 7. Polymers released lysozyme, which digested the opaque bacteria, forming a clear zone around the polymer.

APPLICATIONS OF MACROMOLECULAR POLYMERIC DELIVERY SYSTEMS AND DEMONSTRATION OF BIOLOGICAL ACTIVITY

Over the past five years, we have explored a number of applications of these polymeric delivery systems and have established that the polymers are delivering macromolecules in biologically active form. Applications of these systems include biological use as vehicles in bioassays or in creating

chemical concentration gradients in chemotactic studies, and potential clinical use for continuous insulin delivery or as an improved immunization method.

Biological Assays

The most immediate application of macromolecular polymeric delivery systems has been in the development of biological assays for informational macromolecules. Such molecules (e.g. growth factors) are generally available only in small quantities and diffuse rapidly away from an implant site *in vivo* if injected or delivered by some other means. The polymers, however, maintain the macromolecule at an appropriate *in vivo* site and can provide macromolecules continuously for months, if desired. One example is the development of a bioassay for tumor neovascularization. It has been found that tumors elicit a diffusible material called tumor angiogenesis factor (TAF), which induces new blood vessels to grow from the host. The new vessels are essential for continued tumor growth and therefore purification of TAF is of fundamental interest. To develop an *in vivo* assay for TAF, we implanted ethylene-vinylacetate copolymers in rabbit corneas. In over 200 experiments, slow-release pellets containing crude tumor extracts with TAF activity (M.W. 100,000 [11]) consistently elicited a neovascular response (Figure 5). Furthermore, the rate at which vessels grew in the cornea depended on the quantity (9) and purity of TAF in the polymer.

In addition, these polymers have provided the basis for bioassays for growth factors derived from cartilage (12), the vitrious body (13), and macrophages (14). They also have been used in studies concerning the development of corneal ulcers (15) and in tests exploring the mechanism of vascular regression (16).

Chemotaxis Studies

Chemotaxis, or the movement toward or away from the source of a chemical compound, has been observed in a wide variety of organisms. Although numerous techniques have been employed to create concentration gradients to study this phenomenon, these methods are complicated and lack versatility (17-19). We believed that sustained-release polymers might provide a simple and inexpensive means of creating concentration gradients to study chemotaxis. To examine this possibility, we studied the response of worms (planaria, *Dugesia dorotocephala*) to chemical gradients in an unstabilized aqueous medium. For this purpose, we adapted the T-maze system (Figure 6) of Coward and Johannes,

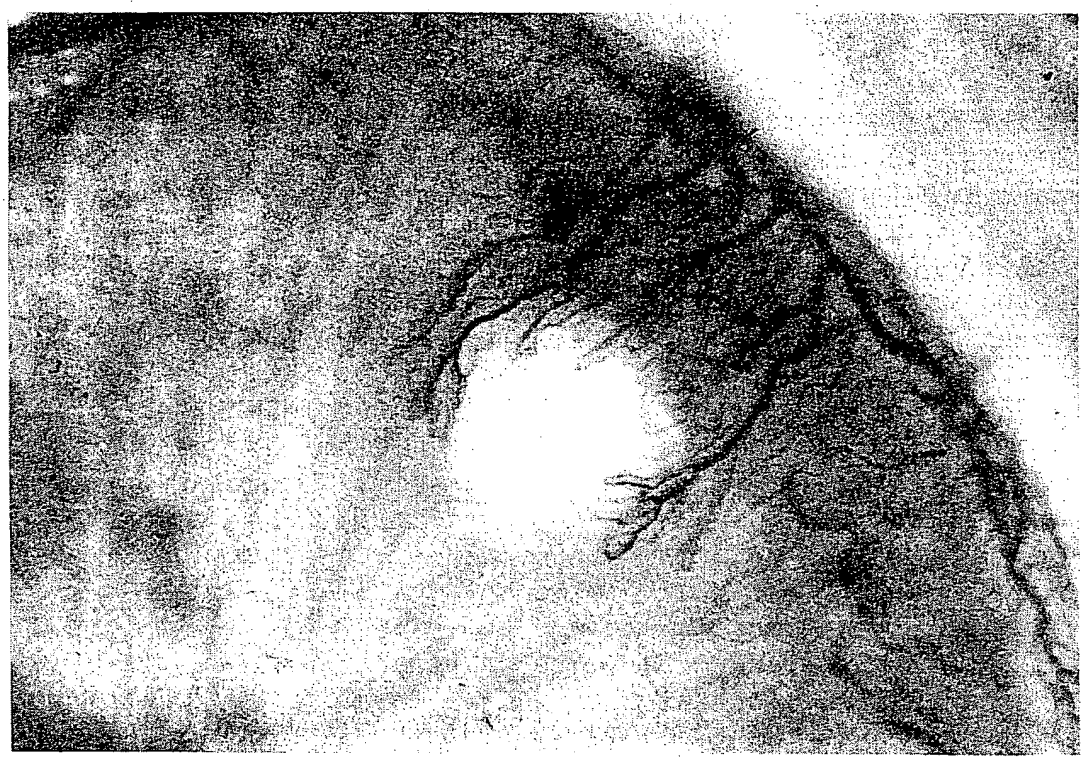

FIGURE 5. Rabbit cornea 20 days after implantation of coated ethylene-vinylacetate copolymer pellet containing tumor angiogenesis factor (TAF). Vessels from the corneal edge grew toward the polymer.

who had previously demonstrated a chemotactic response of the worms toward L-lysine, using synchronized infusion pumps to establish a chemical gradient (20). In 70 tests, we found that the worms consistently migrated to the arm of the maze containing polymers impregnated with L-lysine ($P < 0.001$). They migrated with equal frequency to either arm of the maze if the polymers were empty or contained a control substance (L-glutamate).

In a second set of studies, we explored the use of these polymers as a simple method for investigating bacterial chemotaxis. The responses of three strains of *Escherichia coli* to polymers releasing α-methyl-D,L-aspartate (a nonmetabolizable attractant) into soft agar were examined. Two of the *E. coli* strains, AW405 and AW518, exhibited chemotaxis toward the polymer, as anticipated (Figure 7). The other bacterial mutant, AW539, is defective in taxis toward α-methyl-D,L-aspartate (21) and served as a control; this mutant did not exhibit chemotaxis

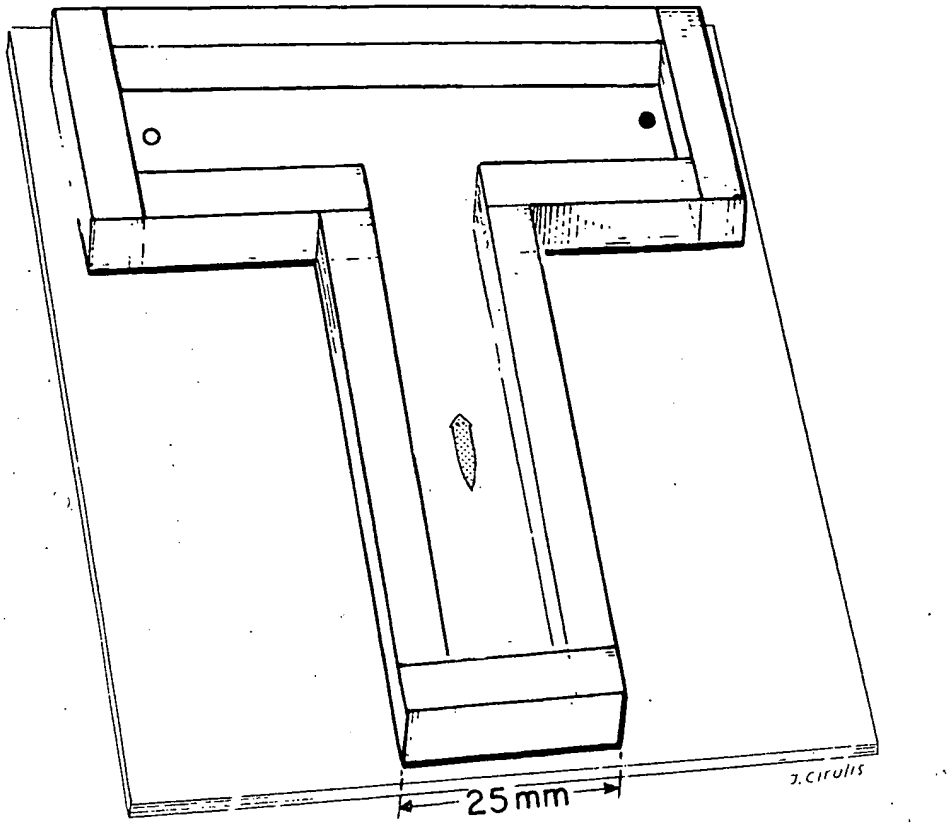

FIGURE 6. T-maze used to assay chemotaxis of planaria. Black dots represent polymers containing a chemotactic factor; white dots indicate empty polymers. The number of times a planaria swam to a particular arm of the T-maze was counted.

(Figure 7). This result has been reproduced in 80 separate tests with these polymers. The entire assay took less than 7 hrs. In addition, in studies of the reusability of polymers, the same polymer consistently elicited chemotaxis in three successive assays after more than 30 days of release into soft agar.

Insulin Delivery

Diabetics normally require insulin injections once or twice daily. Besides the inconvenience, this schedule of insulin administration results in abnormal peaks and valleys in blood glucose levels. Poor control of blood glucose may be responsible, in part, for diabetic complications such as blindness and heart and kidney disease (22).

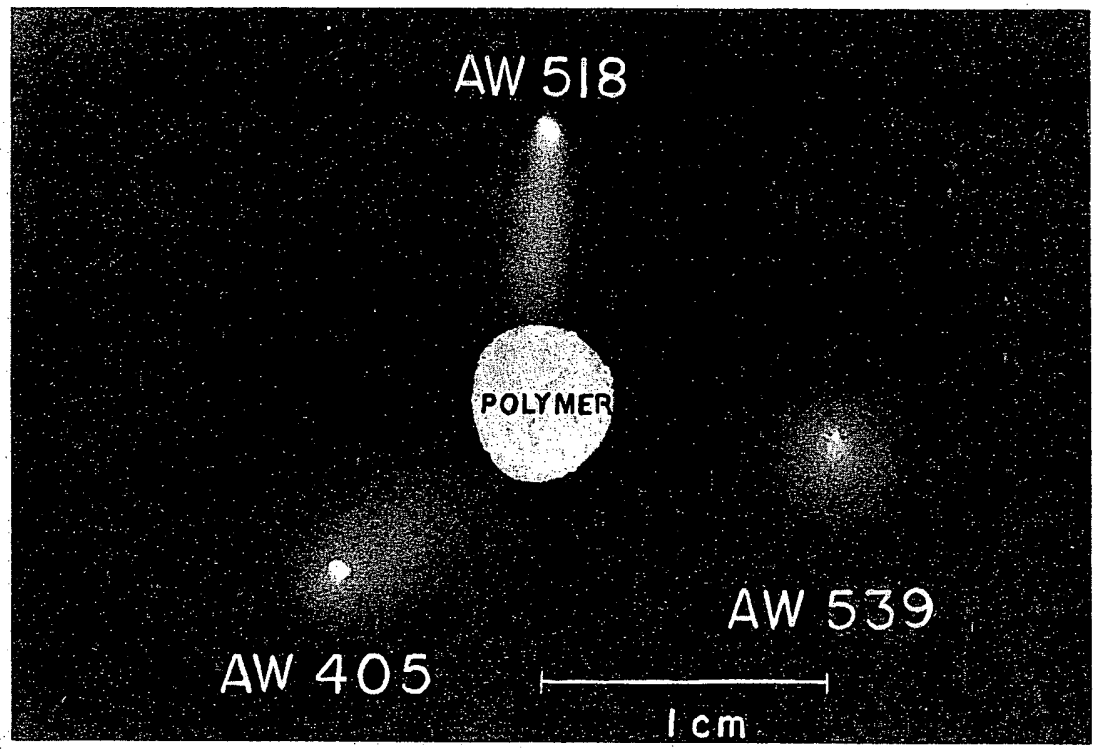

FIGURE 7. Chemotaxis of E. coli mutants toward a polymer containing α-methyl-D,L-aspartate in soft agar. The different responses of these mutants indicated chemotaxis (strain AW518) or no chemotaxis (strain AW539).

The ability of sustained-release polymers containing insulin to maintain normoglycemia was tested in diabetic rats. Male rats (CD strain, Charles River Breeding Laboratories; 21 days old) weighing 150 to 250 g were made diabetic with streptozotocin. Ethylene-vinylacetate copolymer discs (1.3 cm diameter, 1 mm high) containing 100 mg of bovine pancreatic insulin were implanted subcutaneously in the lower abdomen. Implant sites were closed with a Michel wound clip.

The results are summarized in Figure 8. Control animals with empty polymers or without polymers showed consistently high blood glucose levels. In contrast, the rats implanted with insulin polymers showed normal glucose levels for one month. Furthermore, rats in the experimental groups gained weight at a normal rate, whereas growth of the controls was depressed as a result of the disease.

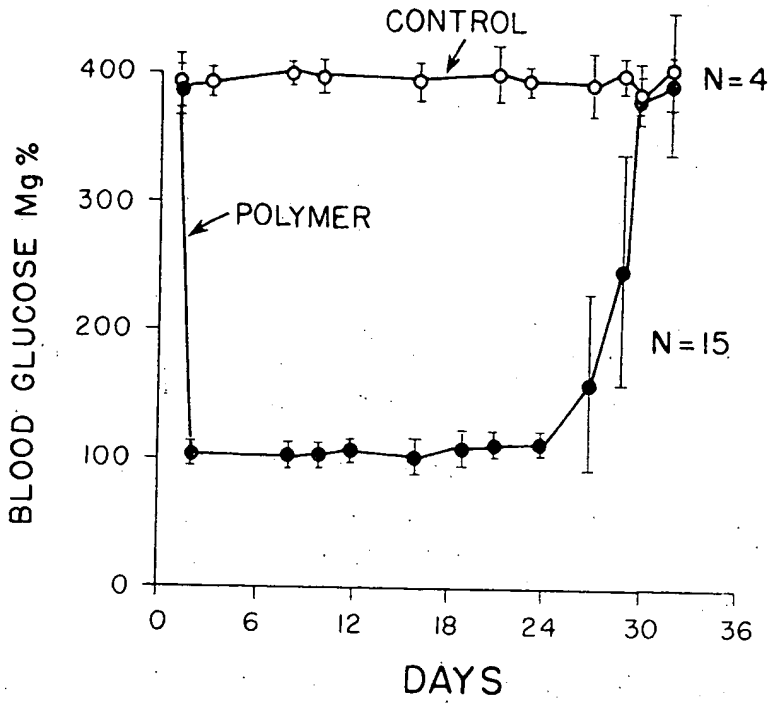

FIGURE 8. Implantation of single insulin-containing polymers into diabetic rats. Controls were diabetic rats receiving empty polymers or no polymers.

Additional experiments monitored variations in blood glucose levels during a one-day period. Figure 9 illustrates variations in blood glucose concentrations on day 16 of treatment. During the 31 hr. study, glucose levels for treated animals were 95 ± 13 mg%; in contrast, the controls maintained a level of 338 ± 61 mg%. Furthermore, treated animals voided approximately 40 ml of urine in 31 hrs. Urine glucose was not detected in the treated animals. Untreated controls voided nearly 200 ml of urine during 31 hrs. and urine glucose concentrations exceeded 500 mg%.

Immunization Procedures

Conventional methods for immunizing both animals and humans generally require multiple injections and often cause tissue irritation (23). In a recent study, we considered the possibility that sustained-release polymers for macromolecules

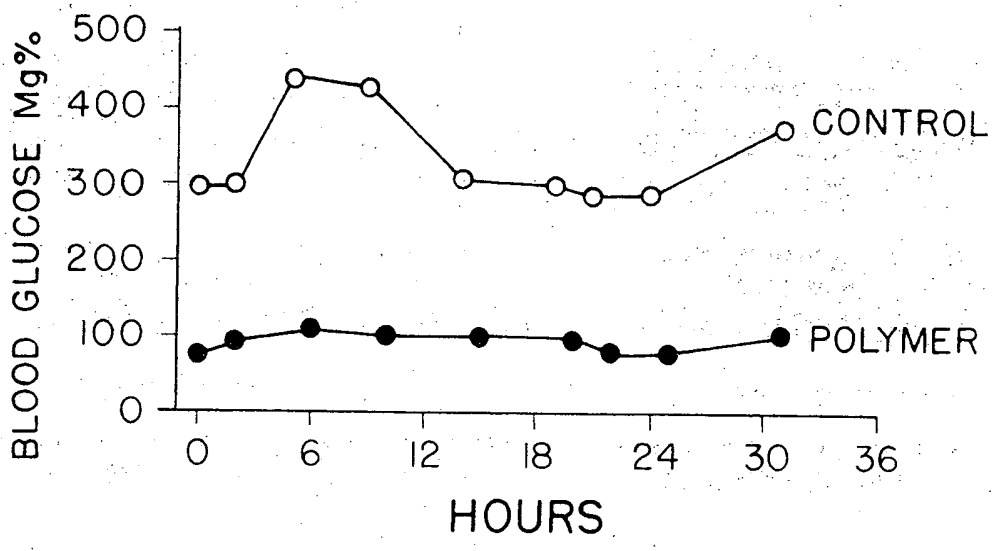

FIGURE 9. Blood glucose determinations made every few hours around the clock for two treated animals and one control animal.

might provide a simple, safe, and effective means of immunization by acting as a series of continuous minishots (24). Ethylene-vinylacetate copolymer pellets containing 100 µg of bovine serum albumin were fabricated according to previously described methods (7) and implanted in C57 black mice. The immune response stimulated by sustained antigen delivery from one pellet was compared to a conventional method of immunization; two injections of bovine serum albumin emulsified in complete Freund's adjuvant (25). The immune response was measured by indirect haemagglutination. The results, summarized in Figure 10, indicated that the immune response induced by the antigen in polymer is comparable or superior to that induced by the same total dose of antigen using the conventional technique. Furthermore, a single polymer pellet caused a sustained immune response for six months. No tissue irritation was observed with the sustained-release system. This immunization procedure is effective for antigens other than albumin and over a wide range of molecular weights (24).

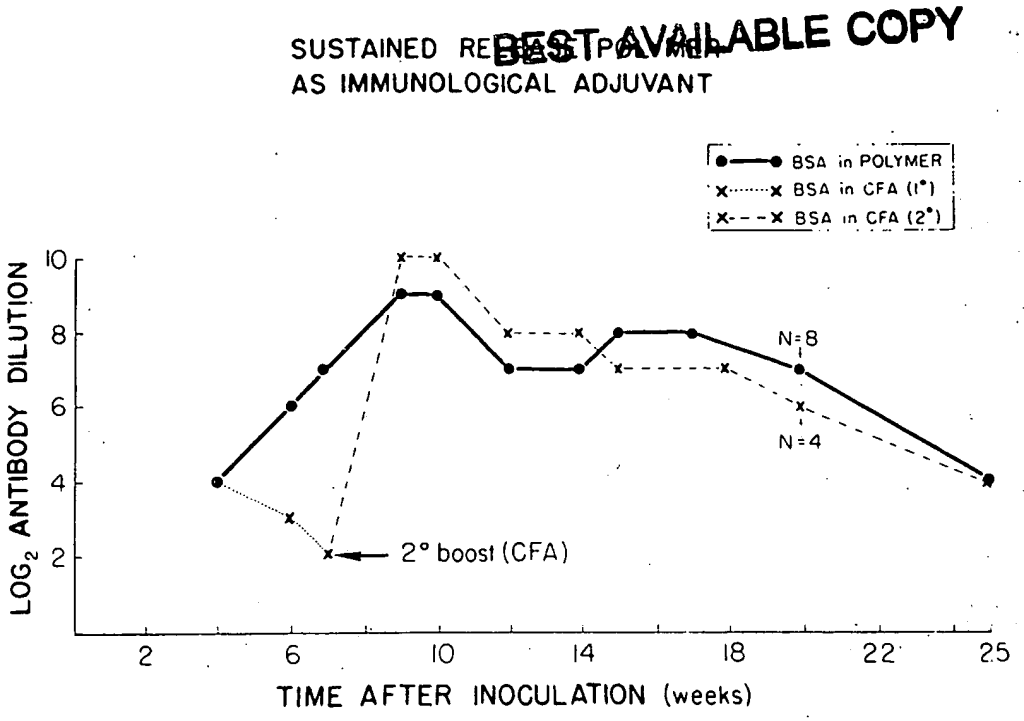

FIGURE 10. Antibody titre in C57 black mice as a function of time, as determined by haemagglutination. The standard deviation on a given point is 1.16.

REPRODUCIBLE PROCEDURES FOR FABRICATING POLYMERIC DELIVERY SYSTEMS AND FACTORS CONTROLLING RELEASE KINETICS

Although our original methods for producing polymeric delivery systems from ethylene-vinylacetate copolymer permitted *sustained* release, the kinetics were often not reproducible; therefore, *controlled* release was not achieved. We concluded that irreproducibility was a result of drug settling and redistribution during casting and drying caused by the insolubility of the incorporated macromolecules in the polymer solvent. At room temperature, the drug migrated vertically and there also was visible lateral motion caused by currents (possible thermal) in the mixture. We have recently developed a low-temperature casting and drying procedure that minimizes this drug movement during matrix formation. This method, described below, produced polymer systems with markedly improved reproducibility of release kinetics.

The achievement of reproducible kinetics enabled us to study the effects of certain fabrication factors, including drug particle size, drug loading, and matrix coating on macromolecular release. The significant effects of these factors on release kinetics suggest possible means of utilizing and modifying macromolecular release systems according to specific needs.

Reproducibility of Release Kinetics

A new procedure for producing polymer release systems with improved kinetic reproducibility is outlined in Figure 11 and described in detail as follows: Ethylene-vinylacetate copolymer (40% vinylacetate by weight) was dissolved in methylene chloride to give a 10% solution (w/v). Protein or other macromolecular powder was sieved to yield particles in a desired size range. A weighed amount of powder from a single size range was added to 15 ml of the polymer solution in a glass vial and the mixture was vortexed for 10 sec to yield a uniform suspension. This mixture was poured quickly into a leveled glass mold (7 x 7 x 0.5 cm), which had been previously cooled on dry ice for 5 min. During precooling, the mold was covered to prevent excess frost formation. After the mixture was poured, the mold remained on dry ice for 10 min. The frozen slab was easily pried loose with a spatula, transferred onto a wire screen, and kept at -20°C for 2 days. The slab was then dried for 2 more days at room temperature in a desiccator kept under a mild, houseline vacuum. Drying caused the slabs to shrink in size to approximately 5 x 5 cm. The central 3 x 3 cm square was excised with a scalpel and straight edge, and further divided into nine 1 x 1 cm squares.

Figure 12 depicts the reproducibility of release kinetics from matrices prepared at low temperature. Three slabs were prepared with bovine serum albumin and all 27 1 x 1 cm squares were measured for release for more than 24 days. The mean daily release rates and their standard deviations are graphed in Figure 12. Standard deviations of release rates were within 15% of the respective means. (Standard deviations of release rates from matrices prepared at room temperature were only within 75%.) In addition, more than 90% of the total release variance was due to variability within a single slab.

Other studies using different proteins, particle sizes, and loadings yielded release reproducibilities consistent with the above observations, with one exception: at high loadings (≥50%), the center square had a significantly slower release rate than the other eight squares from the same slab.

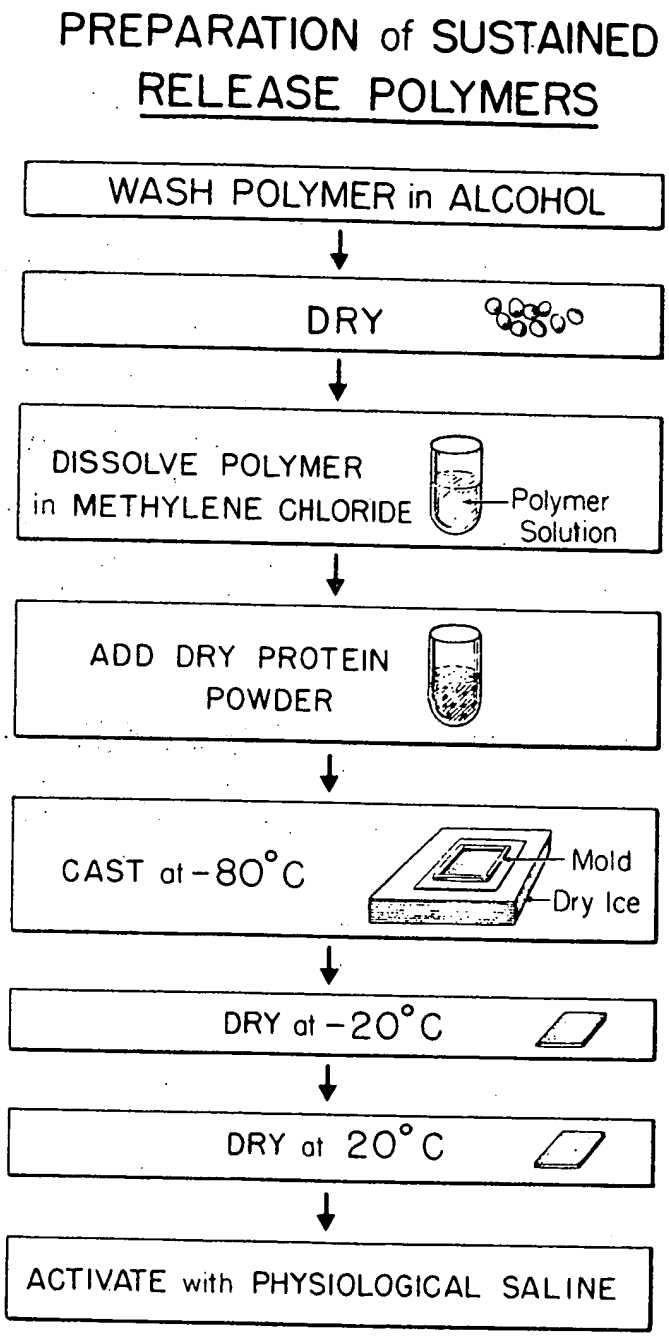

FIGURE 11. Flow diagram describing the preparation of sustained-release polymers composed of ethylene-vinylacetate copolymer. The alcohol wash is only necessary for removing impurities that cause minor inflammation in sensitive tissues.

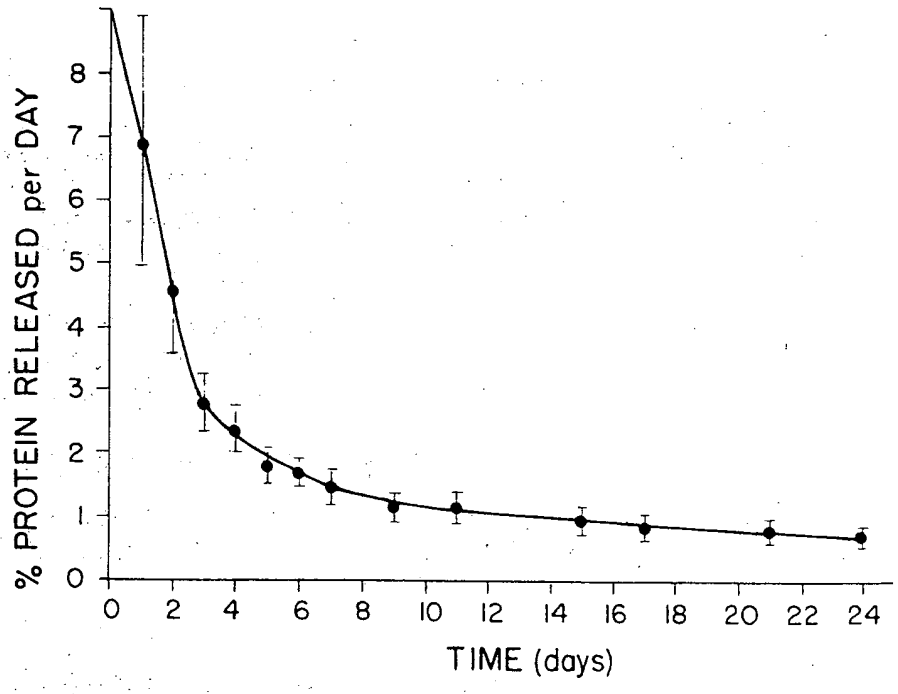

FIGURE 12. Reproducibility of release rates for 27 matrices prepared from three different slabs. The incorporated protein is bovine serum albumin at a particle size of 75-250 μ and a loading of 25%.

Factors Affecting Release Kinetics

Particle size and *loading:* A series of experiments was conducted to examine the effects of particle size and loading on release rates. Examples of our findings are shown in Figures 13 and 14. In general, we observed that increased particle size resulted in increased release rate. In the example shown, a change in particle size altered release rates by a factor of six.

Increases in drug loading uniformly increased release rates (Figure 14). Not only did total drug release increase but the cumulative percent of matrix drug released over time increased. As much as a 50-fold increase in the slopes of percent release was caused by increasing drug loading from 10 to 50% by weight.

Coating: The effect of coating matrices with an additional layer of polymer was examined. Polymeric matrices, 50% insulin by weight, were prepared by the described procedures,

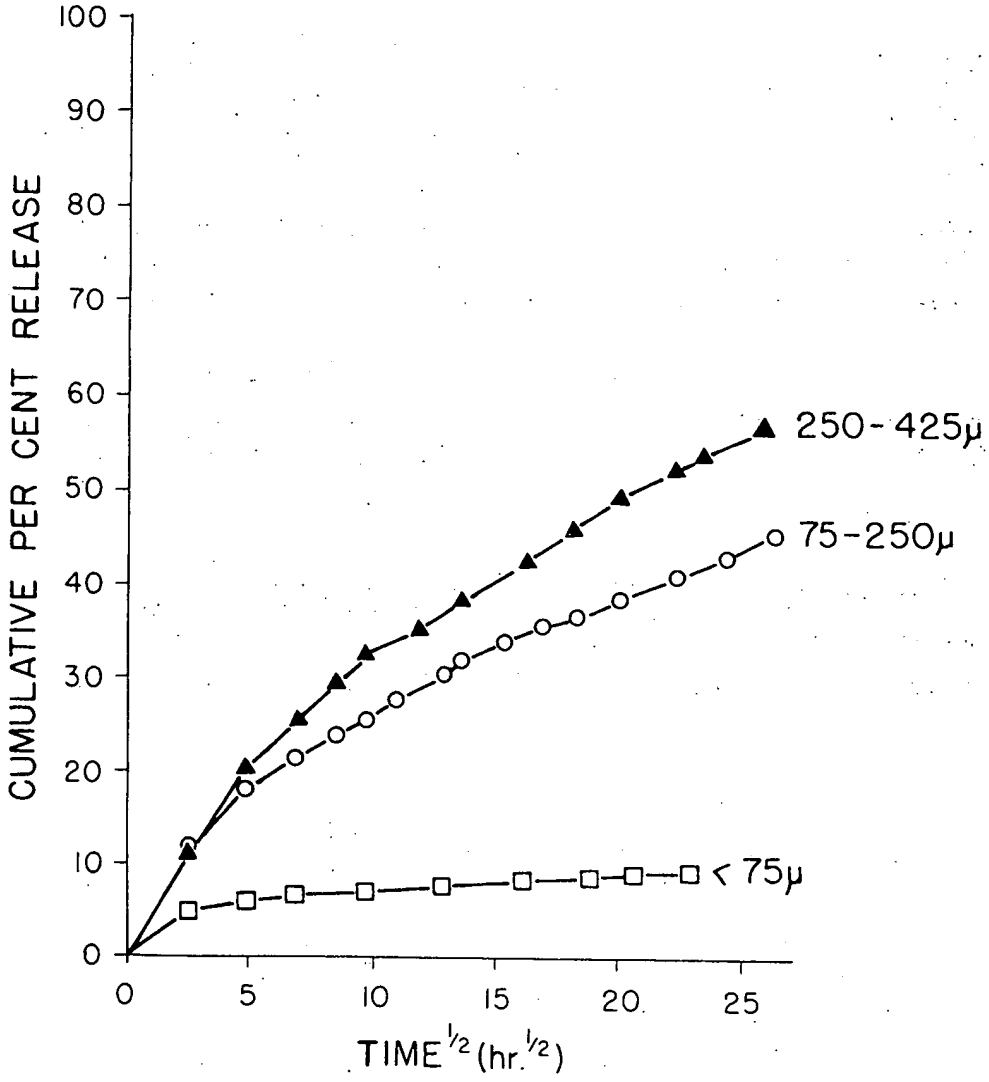

FIGURE 13. Effect of particle size on the cumulative release of bovine serum albumin. The loading is 25%. Each point represents the mean of at least eight samples. Standard deviations are all less than 10% of the respective mean values.

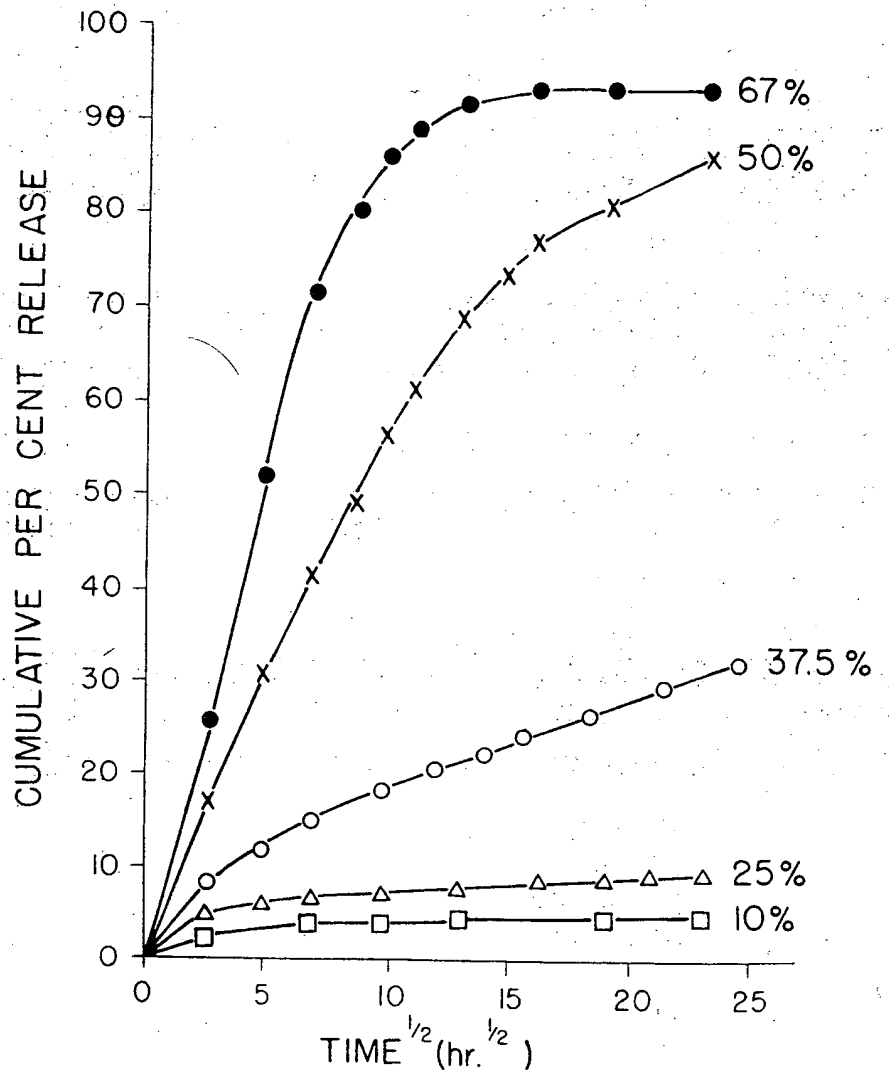

FIGURE 14. Effect of loading on the cumulative release of bovine serum albumin. The particle size is less than 75 μ. Each point represents the mean of at least eight samples. Standard deviations are all less than 10% of the respective mean values.

except that the insulin powder was not sieved. (Commercial insulin powder, with a particle size of <50 μ is more uniform than most protein powder preparations.) After the insulin-polymer matrices were dried and weighed, the squares were coated by dropping each into a vial containing 15 ml of polymer

solution, either 5 or 20% (w/v) ethylene-vinylacetate copolymer in methylene chloride. After 1 min in solution, the square was grasped on its edges with forceps, removed from solution, and held to dry at room temperature for 2 min. The matrix was dried for an additional 24 hrs at room temperature under mild vacuum.

As shown in Figure 15, coating significantly affected drug release rates. Release kinetics decreased with increases in coating solution concentrations. A seven-fold difference in release rates was observed between uncoated samples and samples coated with 20% polymer solution. Standard deviations of cumulative release values were within 15% of the means.

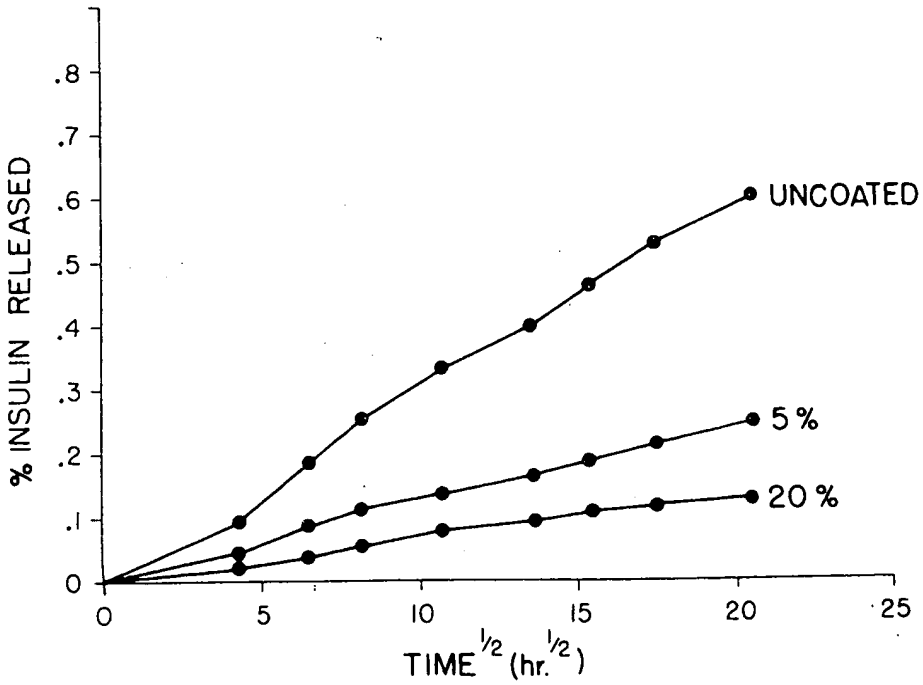

FIGURE 15. Effect of coating on the cumulative release of insulin. Each point represents the mean of eight samples. Standard deviations are all less than 15% of the respective mean values.

DISCUSSION

These studies demonstrate several important applications of macromolecular delivery systems and further elucidate the release properties of these systems. Data obtained in the experiments reported here illustrate that sustained-release systems may be useful in blood glucose control, immunization procedures, bioassays, and chemotaxis studies. These specific release systems were not optimized and it is anticipated that improved systems will yield even more impressive results.

The ability of sustained-release polymers to provide effective alternatives to conventional modes of insulin therapy and immunization procedures in animals indicates the potential clinical importance of these systems. Drugs remain protected in the polymer and are then released in unaltered form. This may be particularly important for the long-term administration of molecules that are rapidly degraded *in vivo* or are available only in small quantities. There are numerous other macromolecules that may eventually be candidates for sustained release, including heparin, a widely used anticoagulant, and interferon, a new anti-viral compound. While the ultimate form of specific slow-release systems may vary, our studies suggest the potential value of sustained macromolecular release for a variety of clinical applications.

Sustained-release polymers also provide a basis for bioassays and chemotaxis experiments, which suggests a range of applications in basic biological studies. Sustained-release polymers possess many advantages over earlier methods of testing informational macromolecules *in vivo* or creating chemical concentration gradients *in vitro* and *in vivo*. Advantages include low cost, ease of fabrication, versatility, ability to localize substances in target areas, and protection from biodegradation.

The kinetic experiments demonstrate the effectiveness of low-temperature fabrication procedures for the incorporation of macromolecules into polymeric matrices. These procedures prevented protein migration during casting and drying of the polymer slabs and resulted in matrices with uniform drug distribution and reproducible release kinetics. Similar low-temperature techniques may prove useful in other systems that require uniform distribution of an insoluble compound in a polymer solution.

The reproducibility of release kinetics for matrices prepared by low-temperature methods has been demonstrated for different proteins and for a range of particle sizes and loadings (26). However, it may be more difficult to uniformly incorporate some macromolecules if their density is much greater than those used in the present study, because high

density may increase particle settling even at low temperatures. This settling may possibly be avoided by more rapid cooling during casting.

There appeared to be three phases of release: 1) a "burst" or initial period of rapid release, 2) a period when release was approximately linear with respect to $time^{1/2}$ and 3) a final period when release tapered off. The burst effect presumably was due to the dissolution of proteins on the surface and cut edges of the matrix. The intermediate phase of release that displayed $time^{1/2}$ kinetics resembled earlier models of release of low molecular weight drugs from granular matrices (27). Because macromolecules are too large to diffuse through a pure polymer film (7), it is possible that sustained release occurs via diffusion through channels in the matrix. The incorporation of the macromolecules during casting may introduce such channels through which the dissolved drug can diffuse. In this case, observed differences in release rates for different proteins would be attributable to differences in protein properties (solubility, diffusivity) and matrix characteristics (porosity, tortuosity).

Our studies demonstrate the marked effect of drug particle size and loading on release kinetics. Release-rate increases caused by increases in particle size may result from the formation of larger channels or pores in the polymer matrix. Similarly, increased loadings may provide simpler pathways (lower tortuosity) and greater porosity for diffusion, both of which would facilitate the movement of water into, and proteins out of, the matrix.

Coating can also be used to control the kinetics of macromolecular release; it may reduce the amount of macromolecule on the matrix surface and may decrease surface access of pores for channeled diffusion. It is assumed that the coating does not cause a complete barrier to form around the matrix because that would prevent any macromolecular diffusion into the surrounding media (7).

The low-temperature fabrication procedures for macromolecular release systems are easy to perform and use standard, inexpensive laboratory apparatus. A wide spectrum of release rates can be achieved by altering drug particle size and loading, and by coating the matrix; therefore, these systems can be modified for various applications. Further work is being directed toward the development of physical and mathematical models to describe and predict macromolecular release kinetics, toward the further exploration of potential applications of these unique delivery systems, and toward the development of zero-order release devices. Thus, although there

are many important problems still to be studied, non-inflammatory, macromolecular delivery systems can now be made simply and reproducibly, and effectively employed in a variety of applications.

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